COROSOLIC ACID FORMULATION AND ITS APPLICATION FOR WEIGHT-LOSS MANAGEMENT AND BLOOD SUGAR BALANCE

FIELD OF THE INVENTION

This invention relates to an improved food supplement formulation including corosolic acid for producing sustained weight-loss management and blood sugar balance effects. This food supplement further also to improve high blood sugar levels in subjects suffering from type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM).

BACKGROUND OF THE INVENTION

The first diagnosis of diabetes dates back to Greece, 2,000 years ago. Blood sugar balance, in general, diabetes, in particular, ever since has been the subject of an increasing scientific study. Diabetes affects 16 million people in the United States alone and it is the fourth leading cause of death. Insulin, the hormone produced by pancreas, regulates the uptake and conversion of sugar into heat energy and muscle power. Diabetes is a metabolic disorder and insufficient insulin production leads to Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM). Lipid metabolism is often deranged in diabetics resulting in weight gain and other complications.

More than half of U.S. adults are overweight (body mass index, BMI >25), [illegible] (BMI >30), and 11% of children and adolescents are overweight. Approximately 300,000 deaths are attributable to obesity annually. Sedentary life style is prevalent and only 24% of U.S. adults exercise the recommended five times per week for at least 30 minutes. Healthy weight maintenance involves a delicate balance between energy intake and energy expenditure.

Glucose is the principal nutrient for energy and daily energy balance between [illegible] and expenditure is a determining factor in body weight stability. A chronic positive energy balance leads

to weight [illegible], while [illegible] accounts for weight loss. Obesity is [illegible] globally and more acute in developed countries due to [illegible] life style and rich diets among both adults and children that lead to deleterious consequences such as obesity, Syndrome X, insulin resistance, diabetes and other health risks (York D, [illegible]. How obesity develops, Endocrine, 13 (2), 143-154, 2[illegible]). Syndrome X is a metabolic disorder characterized by insulin resistance, abdominal obesity, high cholesterol, high blood pressure, high triglyceride and sugar levels. An estimated 20 to 30% of middle-aged Americans suffer from Syndrome X, which is believed to increase the risk of stroke and heart disease. The spread of obesity is [illegible] epidemic in the U.S. and a sensible, sustained weight management is a critical step in this environment (Mokdad AH, [illegible], Bowman BA, Marks JS, Koplan JP. The spread of the obesity, [illegible] in the United States, 1991-1998, JAMA, 282 (16), [illegible], 1999).

Glucose is the most important nutrient for many cells of the body. Glucose transport from the blood into cells, therefore, is one of the most significant functions of all cells and some tissues, such as brain, are [illegible] dependent on glucose as an energy source. Insulin regulates glucose uptake into fat and muscle cells through the recruitment of [illegible] transporter (GLUT)4 from an intracellular membrane [illegible] pool to the plasma membrane. A complex homeostatic mechanism keeps the blood glucose level constant in normal [illegible] cells contain several types of sodium linked glucose [illegible] known as GLUT family. Glucose transporters, [illegible], are especially important for regulation [illegible] in insulin sensitive [illegible] skeletal muscle cells and in fat [illegible] (adipocytes). The pancreatic hormone [illegible] is [illegible] by a cascade of biochemical steps, including activation and translocation of GLUT4 to cell surface, [illegible] transport from blood to cells (Yamasaki Y, [illegible] Insulin signaling on glucose transport system, Eds. Waller [illegible], [illegible]. Plenum Press, New York; Maier VH and Gould GW. [illegible] treatment of 3T3-L1 adipocytes results in [illegible] of GLUT4: implications for

insulin-stimulated glucose transport, Diabetologia, 43, 1273-1281, 2000; Yaworsky K, Somwar R, Ramlal T, Tritschler HJ, Klip A. Engagement of insulin-sensitive pathway in the stimulation of glucose transport by α-lipoic acid in 3T3-L1 adipocytes, Diabetologia, 43, 294-303, 2000).

Numerous groups have been systematically searching for an agent to modify glucose transport activity and to find a natural product useful as an anti-diabetic agent. Various medicinal plants from Asia have been used to treat diabetes and the plants exhibiting hypoglycemic effect include *Momordica Charantia*, *Tinospora Cordifolia*, *Banaba*, etc. (Yamasaki K 1996). Tea preparations from the leaves of *Lagerstroemia Speciosa L.*, traditionally have been used for weight-loss and by diabetics to balance blood sugar levels (Murakami C, Myoga K, Ryoji K, Ohtani K, Kurokawa T, Ishibashi S, Dayrit F, Padolina WG and Yamasaki, K. Screening of plant constituents for effect on glucose transport activity in Ehrlich ascites tumor cells, Chemical and Pharmaceutical Bulletin, 41 (12), 2129-2131, 1993) and in-vitro studies indicate that Corosolic acid extracted from the leaves of *Lagerstroemia Speciosa L.* improves the cellular uptake of glucose (Murakami T. et al. 1993). Further studies in diabetic mice indicate the hypoglycemic effects of leaf-extracts from *Lagerstroemia Speciosa L.* (Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H and Kuroyanagi M. Hypoglycemic effect of extracts from *Lagerstroemia speciosa L.* leaves in genetically diabetic KK-AY mice, Biosci. Biotech. Biochem., 60 (2), 204-208, 1996).

SUMMARY OF THE INVENTION

The present invention comprises a stable and non-toxic Corosolic acid formulation including a soft gel formulation for increased absorption of Corosolic acid into the human body. A preferred soft gel formulation includes Corosolic acid, rice bran oil, and yellow beeswax or silica. The preferred soft gel Corosolic acid formulation is administered thrice a day in dosages of about 1[illegible] mg.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical comparison of the sugar levels in volunteers taking nothing, Corosolic acid in gel form and Corosolic acid in powder form;

Figure 2 is a graph showing the washout rates of blood sugar level vs. time during and after taking gel and powder Corosolic acid;

Figure 3 is a comparison graph showing the blood sugar level vs. time during and after taking gel and powder Corosolic acid;

Figure 4 is a graph showing the washout rates of weight vs. time during and after taking gel and powder Corosolic acid;

Figure 5 is a graphical comparison of the weight of volunteers taking nothing, Corosolic acid in gel form and Corosolic acid in powder form; and

Figure 6 is a graph of weight change vs. dosage of Corosolic acid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Corosolic acid (2-alpha-hydroxyursolic acid, CAS# 52213-27-1; Glucosol™ (trademark of Gel Technologies, Inc. of Los Angeles, CA) is a triterpene having a molecular weight of 743.63 grams and is a lipophilic, plant compound that is extracted from the leaves of *Lagerstroemia Speciosa L.* *Lagerstroemia Speciosa L.* is commonly known as Crape Myrtle and belongs to the botanical family *lythraceae*. It is a very common ornamental deciduous tree that grows in the tropical areas of the globe. Tea preparations from the leaves of *Lagerstroemia Speciosa L.*, traditionally have been used for weight loss and many diabetics to balance blood sugar levels (Murakami et. al., 1997).

Both in-vitro and in-vivo studies on the glucose transporter stimulatory activity of the extract from *Lagerstroemia Speciosa L.*, have been performed recently, including the identification of Corosolic acid (2-alpha-hydroxyursolic acid, CAS# 52213-27-1), a triterpenoid, as the active principle of this extract and its hypoglycemic effect (Matsuda et. al., 1998; Yamasaki, 1996; De Tommasi N, De Simone F, Rastrelli L, Morelli I, Pizza C,

Hypoglyc[illegible] polyhydroxy [illegible] Eriobotrya japonica, Planta Meica, 57, [illegible], 1991; [illegible], F. on the Hypoglycemic Effect of Decoction of [illegible] Lagerstroemia speciosa Leaves (Banaba) Administered Orally. *The Journal of the Philippine Medical Association*, 22, #7, 395402, 1946; [illegible], F. Elimination and Deterioration of Insulin-like Principle in Lagerstroemia speciosa (Banaba). *Acta Medica Philippina*, [illegible]; Garcia, F., and Melencio-Maglalang, P. Application of Banaba (A Botanical Preparation) and S.B. Menus to Diabetics. *The Journal of the Philippine Medical Association*, 33, #1, 7-16, 1957; Garcia, F. Criticisms and Answers on Published Articles [illegible] Banaba Tablets. *The Journal of the Philippine* [illegible], #5, 214-219, 1959; Garcia, L., Peñas, [illegible], [illegible], [illegible], [illegible], [illegible] and Capal, T. Pharmacodynamic [illegible] Clinical Studies on a Crude Drug from Lagerstroemia [illegible]. *The Philippine Journal of Science*, 116, #4, [illegible], 1988; Canal et al., Int. J. Tiss. Reac., 1983, X 2, [illegible]). Furthermore, according to the descriptions in the following [illegible], extracts from these plants administered to rats at [illegible] showed significant reduction in blood sugar levels. Acute toxicity studies in rats based on a single oral limit-dose of [illegible] indicate that corosolic acid is safe and non-toxic.

The [illegible] study was conducted using the soft-gelatin capsule [illegible] Corosolic Acid (Glucosol™) to evaluate the hypoglycemic and weight loss effects in Type 2 diabetics. A [illegible] was conducted in normal subjects to compile [illegible] corosolic acid.

Blood glucose [illegible]:

A group [illegible] with [illegible] type 2 diabetes (six men of age [illegible] and body weight ranges of 171 to 238 pounds and [illegible] in 54 to 70 years of age with a weight range of [illegible]) were given an oral daily dose of 48 mg Glucosol™ [illegible] for 30 days followed by a 45 day wash-[illegible]. [illegible] was followed over to an oral

daily dose [illegible] Glucosol™ in a hard gel capsule formulation for 30 days [illegible] wash-out period. Each volunteer provided a [illegible] in the morning, after an over night fast, seven days [illegible] of the study (-7 day) and on the day of the study (1 day) [illegible] the basal blood glucose levels. Subsequently, [illegible] level and body weight were measured at 15-day intervals [illegible] duration of the study.

Blood glucose [illegible] and weight-loss:

In this 1-day study, at a daily dose of 48 mg of Glucosol™, both soft [illegible] and hard gel formulations show a statistically significant ($p < 0.01$) decrease in blood glucose levels compared [illegible] fasting glucose measurements (Figures 1, 2, and 3). [illegible] basal levels, the relative reduction in blood glucose [illegible] was similar to that observed in the dose-response study; 31.1% decrease in the soft gel and 22.6% decrease in the hard gel formulation. However, compared to the dry-powder hard gel [illegible] formulation, the soft gel form of Glucosol™ shows a significantly ($p < 0.05$) greater ability to lower blood glucose levels. Further, the slow recovery of blood glucose levels during the wash-out period for both formulations suggests an after-effect or memory-effect of Glucosol™, even after the cessation of the daily dose of Glucosol™ which suggests a significant [illegible] daily-dose compliance issue for diabetics.

Concomitant with the control of blood glucose levels, a weight-[illegible] was observed [illegible] of Glucosol™ (Figures 5 and 6). Further, the [illegible] during the wash-out period was significantly [illegible] the after-effect or memory-effect of Glucosol™. [illegible] was also observed during the dose-response study. The differences in weightloss between the soft gel and hard gel formulations are significant at 32 and 48 mg/day Glucosol™ dose (Figure 6).

Acute and [illegible] chromium (Glucosol™) [illegible] daily dose of 48 mg Glucosol™ [illegible] blood glucose levels remain in the

normal [illegible] before, during and after the intake of Glucosol™. [illegible] chemistry and hematology profiles did not [illegible] indicating the safety profile of Glucosol™. The only significant finding is a weight loss observed [illegible] Glucosol™ at 48 mg per day for 90 days. [illegible] 1.25 + 0.6 pounds after 15 days [illegible] after 90 day use of Glucosol™.

Therefore, oral formulation of leaf extract of *Lagerstroemia speciosa L.* standardized to 1% Corosolic acid (Glucosol™) exert a marked [illegible] in type 2 diabetics and also a significant [illegible] weight-loss without any adverse effects. Further, the results of this study indicate that Glucosol™ does not alter either the [illegible] of blood sugar in non-diabetic [illegible], which is responsible for weight-loss effect.

Glucosol™ [illegible] in soft gel capsule demonstrated a significant [illegible] weight-loss effect compared to Glucosol™ formulated in a dry-powder hard gelatin capsule. This is because the triterpene active ingredient in Glucosol™ is [illegible] and better absorbed in an oil-based soft gelatin capsule formulation.

Although Glucosol™ showed a significant dose-response relationship [illegible] up to 48 mg per day, the top of the dose-response curve may not have been achieved so the maximum dose to achieve a [illegible] response is unknown.

It is an objective of the present invention to provide an improved formulation of corosolic acid, including a soft gel formulation, that provides enhanced and sustained weight-loss and an optimal dose-response curve. To this end, this formulation contains [illegible] standardized to 1% Corosolic acid (Glucosol™) [illegible].

It is a further objective of the present invention to provide a soft gel formulation [illegible] administration that produces [illegible].

The soft gel formulation comprises the following sequence of ingredients.

1. [illegible]

2. Addition [illegible] silica.

3. Simultaneously [illegible] vacuum [illegible] following ingredient: Glucosol™ [illegible] chromic [illegible] chromic acid but an aqueous [illegible] same effect).

4. Blending [illegible] ingredients.

5. Cooling [illegible] temperature (about 22 °C).

6. Thereon [illegible] gas evacuation of the container.

7. Soft gel [illegible] above mixture.

In summary, [illegible] in-vitro, pre-clinical (animal) and clinical studies [illegible] preparations of *Lagerstroemia speciosa L*, [illegible] beneficial effects of blood-sugar lowering and anecdotal [illegible] effects. Present clinical studies establish [illegible] of *Lagerstroemia speciosa* L. standardized [illegible] chromic acid (Glucosol™) formulated into a soft gelatin [illegible] form. Additional studies with this new formulation [illegible] suggest improved bioavailability and absorption [illegible] acid in an oil-based soft gel capsule formulation [illegible] water based gelatin capsule formulation.

In addition, [illegible] may also incorporate an extract of [illegible], known to be helpful for weight loss through [illegible], as an additional ingredient. The present [illegible] include a multi item formulation, with the addition [illegible] Vitamin C and E, B complex vitamins, as well as [illegible] Alpha Lipoic Acid, CoQ , and the mineral chromium, which [illegible] in a balanced weight loss program.

Thus [illegible] described novel formulations, methods, and [illegible], which fulfill all the objects and advantages sought therefor. Many changes, modifications, variations and applications [illegible] formulation will become apparent to those skilled in the art after consideration of the specification and the accompanying [illegible] changes, modifications, alterations and other uses and applications which do not depart from the spirit and scope [illegible] are deemed covered by the invention which is limited only by the claims which follow: